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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,987	03/05/2002	Robert B. Dickson	P 0280712 DIRO421009	4488

909 7590 01/04/2006

PILLSBURY WINTHROP SHAW PITTMAN, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 01/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,987	DICKSON ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *14 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *34-36,38-44,48 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *34-36,38-44,48 and 49* is/are rejected.

7)☐ Claim(s) *40* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/21/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Election filed October 14, 2005 in response to the Office Action of September 15, 2005 is acknowledged and has been entered. Claims 34-36, 38-44 and 48-49 are pending in the application. Claims 34-36, 38-44 and 48-49 are currently under prosecution.

2. Applicants election, without traverse, of Group 1, Claims 34-36, 38-44, 48-49 is acknowledged.

Claim Objections

3. It is noted that claim 40 is objected to because it is a substantial duplicate of claim 39 from which it depends. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to reject the other as being a substantial duplicate of the allowed claim. MPEP § 706.03(k). The claims are substantial duplicates because no activated matriptase other than the two chain matriptase, nor any inactive matriptase other than single-chain matriptase is taught in the specification or known in the art. If claim 39 becomes allowable, claim 40 will be rejected under 35 USC 101 as a substantial duplicate of claim 39.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 34-36, 38-44, 48-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s)

contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of treating a malignant cancer in a subject wherein the malignant cancer is characterized by the presence of activated matriptase comprising obtaining a biological sample from the patient, exposing the sample to a detectable agent that recognizes and binds to activated matriptase, detecting complex and administering to the subject an antibody that blocks the activity of active matriptase, wherein the matriptase that characterizes the malignant cancer is produced by cells of an epithelial tissue, breast cancer, wherein the agent does not bind to inactive matriptase, wherein the detectable agent is labeled with a label, wherein the biological sample is a biopsy, a nipple aspirate or body fluid that has come into contact with the tumor, wherein the antibody that blocks the active maltriptase binds specifically to and directly blocks the activity of the activated matriptase.

The specification teaches that the invention relates to the field of treatment of cancer, particularly breast cancer through the inhibition of matriptase (para 0002 of the published application). The specification teaches that activated matriptase can, activate pro-uPA, a major stromal ECM-degrading protease system, HGF/SF, a prominent stromal-derived epithelial motility factor in the close vicinity of the cell surfaces, and PAR2, a cell surface receptor and that the presence of the Kunitz-type inhibitor, HAI-I, prevents prolonged matriptase proteolytic activity. However, **future studies will be required to establish a more direct relationship between matriptase activation, ECM degradation, and epithelial motility** (emphasis added, para 0098 of the published application). In particular, as

drawn to the HAI-I inhibitor, the specification teaches that the ratio of Matriptase to HAI-1 varies among tumors of breast and gynecological origin, and warrants **further study to determine if a trend in the matriptase to HAI-1 ratio, assessed in a much larger set of tumors, correlates with pathological grade or stage of the tumors, or with clinical measures of outcome such as disease-free and overall survival or response to chemotherapy** (emphasis added). Such studies are currently in progress (para 0071 of the published application).

Matriptase **may** (emphasis added) be activated *in vivo* by the contact of blood with epithelial surfaces (para 0098 of the published application). The specification speculates that as epithelial cells acquire malignant transformation, they **may** (emphasis added) lose transient regulation of the activation of matriptase, but gain constitutive expression of the proteolytic active form of matriptase on their surface (para 0095 of the published application). In addition, the expression pattern of matriptase in primary breast cancers suggests that this protease system is an epithelial-derived system that **may** (emphasis added) activate stromal-derived proteases such as uPA, and growth/motility factors such as HGF/SF, on the surface of breast cancer cells, enhancing their growth and/or invasive properties. Therefore, matriptase **may** (emphasis added) represent an important link in our understanding of how stromally-derived proteases and growth/motility factors may be activated on the surface of normal breast epithelial cells or breast cancer cells. Within a breast tumor, such activity **may** (emphasis added) contribute to the tumorigenic and metastatic properties of breast cancer cells (para 0072 of the published application). Further, the specification teaches that activated matriptase is removed from the cell surface by ectodomain shedding, providing an additional means to regulate the amount of protease and the degree of proteolytic activity on

the surfaces of epithelial cells (para 0097 of the published application). Further, the data presented in the specification makes clear that both matriptase and its cognate inhibitor, HAI-1 are shed upon matriptase activation (para 0091 of the published application.

Finally, although the specification hypothesizes that because matriptase is a membrane protease expressed on the surface of a variety of epithelial cells, where it can function as an activator of stromal-derived effectors involved in tissue remodeling, that matriptase serves as an activator of important effector molecules involved in a variety physiological and pathological processes, such as tissue remodeling, inflammation and cancer invasion and metastasis (para 0101 of the published application). The specification also teaches that the results disclosed in the instant specification suggest that **if** (emphasis added) the catalytic activity of the serine protease matriptase is important for the growth and/or invasion of breast cancer cells in human breast tumors, then the increased activity of the protease in breast cancer is likely due to mechanisms other than a simple increase in matriptase protein or mRNA. The specification goes on to speculate that an increase in matriptase activity could be manifested in multiple ways, for example, by an increase in the matriptase/inhibitor ratio within a tumor, tipping the balance in favor of the protease relative to the inhibitor, or by an increase in the activation of matriptase on the cell surface by proteolytic cleavage. However, it is noted that the specification clearly teaches that at the time the invention was made, the participation of the complex in cancer etiology was unknown and warranted further study. In addition, no guidance is provided either in the specification or the art of record drawn to increased activation of the enzyme in cancer tissues compared to normal controls. Further, the specification acknowledges that like many other

proteases, matriptase requires proteolytic cleavage from a one-chain latent form to a two-chain active form, an event that is not measured by the immunohistochemistry or in situ hybridization assays presented in this paper (para 0070 of the published application).

One cannot extrapolate the teaching of the specification to the enablement of the claims because as clearly stated in the specification, it was unknown at the time the invention was made, whether or not the catalytic activity of the serine protease matriptase is important for the growth and/or invasion of breast cancer cells in human breast tumors or in any other cancer cell type. Further, even if it were to be found that activated matriptase is in any way associated with the growth and/or invasion of cancer cells, the art recognizes that the treatment of cancer arts are highly unpredictable. In particular, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that administration of an antibody that blocks the activity of active matriptase will function as claimed in the treatment of a malignant cancer based only on the hypothesis that because matriptase can activate stromal-derived effectors involved in tissue remodeling, and that as epithelial cells acquire malignant transformation they **may** (emphasis added) lose transient regulation of the activation of matriptase, but gain constitutive expression of the proteolytic active form of matriptase on their surface (para 0095 of the

published application), and that such activity **may** (emphasis added) contribute to the tumorigenic and metastatic properties of breast cancer cells, that activated matriptase is somehow involved in the etiology of cancer and could serve as an effective target for the treatment of cancer. In addition, the association of activated matriptase with its cognate inhibitor HAI-I is well known in the art. Although the specification teaches that ratio of Matriptase to HAI-1 varies among tumors of breast and gynecological origin, the specification also teaches that studies to further characterize the ratio of the two proteins and the meaning of the ratio for cancer etiology are currently underway. Again, the specification clearly teaches that, if the catalytic activity of the serine protease matriptase is important for the growth and/or invasion of breast cancer cells in human breast tumors, or in fact any tumors, then among other mechanisms leading to the loss of regulation of the serine proteases, that will need to be investigated is the matriptase/inhibitor ratio. Thus, it cannot be predicted from the information in the specification whether or not matriptase is in any way associated with the etiology of any cancer. Further, given that it is known that the cognate inhibitor binds to activated matriptase, given that it is known that both HAI-I and activated matriptase are shed from the cells, it would be reasonable to expect that the activated matriptase is inhibited by its cognate inhibitor and it would not be expected that the administration of an antibody that inhibits activated matriptase on an already inhibited serine protease would have any effect on activity of matriptase or that it would function as claimed in the treatment of cancer.

Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the

reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by anticancer agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat anticancer treatment strategies and if this is true, designing effective anticancer regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that invention will function as claimed. In addition, Hartwell et al (Science, 1997, 278:64-1068) teach that an effective anti-cancer therapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065). This teaching is critical to the instant invention given that the specification clearly teaches that matriptase is expressed on not only granulocytes, a subpopulation of leukocytes important in host immune response, but also on vesicular smooth muscle cells *in vivo* (paras 0034-0035 of the published application). Given that the specification clearly teaches that there is a serum derived inducer of maltriptase activation (paras 0036-0040 of the published application) it would be expected that these cells

would also express activated maltriptase, thus the claimed anti-cancer therapeutic antibody would not be an effective anti-cancer therapeutic per Hartwell et al because it would not selectively kill tumor cells. Further, anti-tumor antibodies must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The antibodies may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the antibody. In addition, the antibodies may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the antibody has no effect. This is clearly critical to the instant invention given that, as set forth above, it would be expected that not only granulocytes but also smooth muscle cells will produce activated maltriptase and thus the antibody would be sequestered. Further, given that the specification clearly teaches that a serum factor activates matriptase and that the activation of matriptase is accompanied by the shedding of activated matriptase from cells it is clear that not only the tumors but also the other physiological sites where serum factor activated matriptase would be found would be shedding the activated matriptase and again the antibody therapeutic would be sequestered and it could not be predicted that a large enough local concentration could be established to effectively treat a malignant tumor. Again, because of the known unpredictability of the art, in the absence of experimental evidence, no one

skilled in the art would accept the assertion that administration of an antibody that blocks the activity of active maltriptase will function as claimed in the treatment of a malignant cancer based only on the hypothesis that because matriptase can activate stromal-derived effectors involved in tissue remodeling, and that as epithelial cells acquire malignant transformation they **may** (emphasis added) lose transient regulation of the activation of matriptase, but gain constitutive expression of the proteolytic active form of matriptase on their and that such activity **may** (emphasis added) contribute to the tumorigenic and metastatic properties of breast cancer cells, that activated matriptase is somehow involved in the etiology of cancer and could serve as an effective target for the treatment of cancer.

Finally, one cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide any guidance on whether activated matriptase is present on a sufficient number of cancer cells to allow for successful therapeutic targeting. This is absolutely critical because as set forth above, it is known in the art that matriptase is shed upon activation. In particular, White et al. (2001, Ann. Rev. Med., 2001, 52:125-145), teaches that, for successful immunotherapy, besides specificity of the antibody for the antigen, other properties of the antigen should be considered including the following: (1) the antigen should be present on all or near all of the malignant cells to allow effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating; and (2) whether the antigens are shed, modulated or internalized influences the effectiveness of the administered immunotherapy (p. 126, second paragraph). Additionally, antigen downregulation, (for example through the shedding as clearly exemplified by the specification) can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p. 126,

paragraph before last). Thus, given the known shedding of the enzyme, it cannot be predicted if the activated matriptase is present on a sufficient number of cancer cells, and in sufficient quantity, to allow for successful therapeutic targeting of the cancer.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as claimed with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

5. If Applicant were able to overcome the rejections set forth above, Claims 34, 3638-44, 48-49 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating epithelial malignant cancers, does not reasonably provide enablement for a method for treating malignant cancers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method for treating malignant cancers in a subject wherein the malignant cancer is characterized by the presence of activated matriptase.

The specification teaches as set forth above and further teaches that matriptase is an epithelial, membrane-bound, serine protease and that it may be activated *in vivo* by the contact of blood with epithelial surfaces (para 0098 of the published application). Further, the expression of matriptase correlates with the

expression of markers of an epithelial phenotype but not other phenotypes (para 0066 of the published application).

One cannot extrapolate the teaching of the specification to the claims because it is clear that activated matriptase is found associated only with tumors of epithelial origin. In the absence of a teaching that activated matriptase is found in association with other tumor types, no one of ordinary skill in the art would believe it more likely than not that the invention would function as broadly claimed. In particular as drawn to claim 36, although claim 36 is drawn to a malignant cancer present in the breast, it is well known in the art, as taught by Scott-Conner et al (http://www.vh.org/adult/provider/surgery/Metastases/Metastases.html), first published in May 1997, that virtually all malignancies have been reported to metastasize to breast (see legend for Figure 2). Further, as taught by Tabor's Cyclopedic Medical Dictionary (1985, F.A. Davis Company, Philadelphia, p. 274) epithelial cancers comprise only a subset of cancers wherein cancers comprises a broad group of malignant neoplasms divided into two categories, carcinoma and sarcoma which originate in different tissues. Thus, it cannot be predicted that a malignant cancer present in a breast of a subject would in fact be an epithelial-tissue derived cancer and if not an epithelial-tissue derived cancer, one would not know how to use the claimed invention.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as claimed with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

6. Claims 34-36, 48-49 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 34-36, 48-49 are drawn to a method using a detectable agent that recognizes and binds to activated matriptase. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of a detectable agent that recognizes and binds to activated matriptase, per Lilly by structurally describing a representative number of a detectable agent that recognizes and binds to activated matriptase or by describing "structural features common to the members of the genus, which features constitute a substantial

portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the detectable agent required to practice the method of claim 1 in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any detectable agent other than an antibody, nor does the specification provide any partial structure of detectable agent other than an antibody, nor any physical or chemical characteristics of the detectable agent other than an antibody nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single detectable agent which is an antibody, this does not provide a description of detectable agent which functions as claimed would satisfy the standard set out in Enzo.

The specification also fails to describe the detectable agent by the test set out in Lilly. The specification describes only a single detectable agent, an antibody. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the detectable agent that is required to practice the claimed invention. Since the specification fails to adequately describe the product, it also fails to adequately describe the method of using the product.

7. Claim 41 is rejected under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

The claim is drawn to monoclonal antibody M69.

It is unclear if a cell line which produces an antibody having the exact structural and chemical identity of M69 is known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to a hybridoma cell line producing monoclonal antibody M69, it would not be possible to practice the claimed invention. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242

(William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species, UC28A 3-1 G2. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. ' 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Applicant has not disclosed the deposit of hybridoma cell lines that would reproduce the antibody species, M69.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for

completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of the deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

8. If Applicant were able to overcome the rejections set forth above, Claims 34-36, 38, 42-44, 48-49 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating malignant cancers with an antibody that binds to activated matriptase but not to inactive matriptase wherein said antibody blocks the activity of activated matriptase, does not reasonably provide enablement for a method for treating malignant cancers with antibody that blocks the activity of active matriptase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method of treating a malignant cancer in a subject wherein the malignant cancer is characterized by the presence of activated matriptase comprising administering to the subject an antibody that blocks the activity of active matriptase.

The specification teaches production of mAbs directed against both the inactive 70 kD form and the activated two-chain form of matriptase. The majority of the anti-matriptase mAbs produced showed immunoreactivity against both the

two-chain active and the single-chain inactive forms of matriptase. In contrast, mAbs M123 and M69 only recognized the two-chain form of matriptase but not the single-chain form. (para 0028 of the published application).

One cannot extrapolate the teaching of the specification to the scope of the claims because it is clear, as set forth above, that critical to the instant invention is the ability of the therapeutic antibody to reach its target. In the absence of activated matriptase selectivity, the therapeutic antibody would be absorbed by fluids, cells and tissues where the antibody has no effect. Again, as set forth above, anti-matriptase non-specificity in combination with the art known expression of matriptase not only on granulocytes but also on smooth muscle cells and the shedding of activated matriptase would be expected to result in sequestration of the antibody therapeutic and it could not be predicted that a large enough local concentration could be established to effectively treat a malignant tumor.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as claimed with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

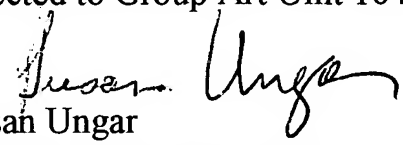
9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787 The fax phone number for this Art Unit is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.



Susan Ungar
Primary Patent Examiner
December 21, 2005